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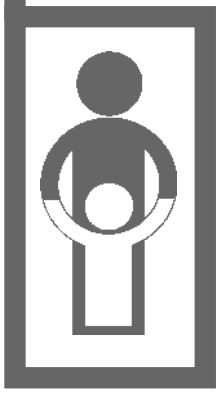
Report of the first meeting of the Steering Committee on Immunization Safety

Geneva, 25-26 October 1999



Immunization Safety Priority Project

DEPARTMENT OF VACCINES AND BIOLOGICALS

World Health Organization
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Safe Injection Global Network (SIGN)
United Nations Population Fund (UNFPA)
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and, most importantly, the national immunization programmes.

The Immunization Safety Priority Project would appreciate being informed of activities related to its mission and to learn of individual or institutional interest in collaborating with the Project.

Visit our web page: http://www.who.int/vaccines-diseases/safety/

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Copies may be requested from:
World Health Organization
Department of Vaccines and Biologicals
CH-1211 Geneva 27, Switzerland
• *Fax:* +22 791 4193/4192 • *E-mail:* vaccines@who.ch •

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Abbreviations

AD	auto-disable
AEFI	adverse event following immunization
BCG	bacillus Calmette-Guérin
BCT	Department of Blood Safety and Clinical Technology (WHO)
CDC	United States Centers for Disease Control and Prevention
DT	diphtheria-tetanus
DTP	diphtheria-tetanus-pertussis
EDM	Department of Essential Drugs and Medicines Policy (WHO)
EIP	Evidence and Information for Policy Cluster (WHO)
EPI	Expanded Programme on Immunization
GAVI	Global Alliance for Vaccines and Immunization
GMP	good manufacturing practice
HIV	human immunodeficiency virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HTP	Health Technology and Pharmaceuticals Cluster (WHO)
NCL	national control laboratory
NGO	nongovernmental organization
NRA	national regulatory authority
OPV	oral polio vaccine
SDE	Sustainable Development and Healthy Environments Cluster (WHO)
SIGN	Safe Injection Global Network
TST	Time-steam saturation-temperature indicator
TT	tetanus toxoid
USAID	United States Agency for International Development
V&B	Department of Vaccines and Biologicals (WHO)
WHO	World Health Organization

Preface

Today, immunization programmes are facing important challenges with respect to safety. Examples of these challenges are the fact that up to one-third of immunization injections are not carried out in a way that guarantees sterility, and that vaccine safety issues and related rumours are poorly understood and handled by those in charge of the immunization programmes.

Immunization Safety has therefore been chosen as a Priority Project of the WHO Department of Vaccines and Biologicals, to strengthen and optimize the impact of immunization services as part of health delivery systems. The ultimate goal is to enable national immunization programmes to prevent, or detect as early as possible and quickly respond to adverse events to minimize their negative impact on health and on immunization programmes. Countries are therefore the primary focus for the target of developing a sustained, comprehensive system to ensure a culture of immunization safety globally.

The Steering Committee on Immunization Safety was formed to provide advice on the strategic activities, constraints and requirements to accomplish the goals of the Priority Project.

The first meeting of the Committee took place at WHO/HQ in Geneva on 25-26 October 1999. The programme and list of participants can be found in Annex 1 and 2 respectively.

Part I of this report places the establishment of the Committee within the context of WHO's activities in immunization. This is followed in Part II by a summary of the presentations made and discussion during the course of the meeting. The recommendations and conclusions of the Committee appear separately in Part III.

Part I: Introduction

I.1 Opening remarks

Dr Michael Scholtz, Executive Director of the Health Technology and Pharmaceuticals Cluster (HTP) of WHO opened the meeting and welcomed participants to this first meeting of the Steering Committee on Immunization Safety. He emphasized that the impetus for establishing this Committee stemmed from the firm belief of WHO, including HTP, in safety issues, a concern which transcended all HTP departments: Blood Safety and Clinical Technology (the Safe Injection Global Network and World Health Day 2000 devoted to blood safety); Essential Drugs and Medicines Policy (the international drug monitoring programme); and the cross-cutting Vaccines and Biologicals Immunization Safety Priority Project.

Issues surrounding immunization safety are indeed wide ranging, with specific needs varying across regions and countries. Some countries still require solutions to primary problems such as access to electricity supply for vaccine storage and the introduction of auto-disable syringes to improve injection safety, whilst others lack strategies to introduce effectively new vaccines and delivery system technologies.

Dr Scholtz highlighted the many serious challenges facing immunization systems today, ranging from lack of access to the safe delivery of vaccines and vaccination technologies, to the inability of "front-line" health care providers to deal with the attention given to adverse events following immunization. From a health population perspective, the tolerance for risk associated with immunization programmes is indeed low, principally because the intervention is delivered to large cohorts of healthy children. It is often difficult to explain, said Dr Scholtz, the difference between a causal and a temporal association between the administration of a vaccine and an incident that might follow the immunization. Negative publicity associated with adverse events following immunization undermines public confidence in immunization programmes. Promotion and advocacy of immunization safety, he concluded, was therefore essential in maintaining the existing and potential benefits of vaccination programmes.

The Executive Director looked forward to learning of the recommendations of the Steering Committee on Immunization Safety to bridge any gaps for WHO to ensure maximum safety in such a key health intervention as immunization.

I.2 Overview of the WHO Department of Vaccines and Biologicals and its participation in the Global Alliance for Vaccines and Immunization

Dr Maureen Birmingham, on behalf of the Director of the WHO Department of Vaccines and Biologicals, presented the strategic structure of V&B within the context of the recently restructured WHO, and introduced the newly formed Global Alliance for Vaccines and Immunization (GAVI).

The draft V&B Strategic Plan highlights its mission – *a world in which all people at risk are protected against vaccine-preventable diseases* – and the three overall objectives chosen to achieve this mission, namely:

1) Innovation: to research, develop and introduce new vaccines, biologicals, related strategies and technologies to reduce the burden of diseases of public health importance.

2) Immunization Systems: to strengthen and optimize the impact of immunization services as a component of health systems.

3) Accelerated Disease Control: to control, eliminate and eradicate priority diseases through the use of routine immunization services and supplementary delivery strategies.

Each objective has a priority project to champion its targets, and all five teams in the Department contribute to the three objectives and priority projects from their own specific focus (see Annex 3). The *Immunization Safety Priority Project* is the focus of the Immunization Systems objective.

Dr Birmingham went on to summarize progress in establishing the Global Alliance for Vaccines and Immunization, in which WHO is a key partner. The mission of this new initiative is "*to save children's lives and protect people's health through the widespread use of vaccines*". She drew attention to the focus of GAVI to make available existing vaccines to disadvantaged countries, and to accelerate the development and introduction of new and "orphan" vaccines into the developing world. A key strategy in achieving these aims will be to make immunization coverage a centrepiece in the design and assessment of international development efforts.

Although the programme is still in its infancy, Dr Birmingham provided an outline of the intended structure of GAVI and its modus operandi. An appointed Board, made up of representatives of the partners, will be supported by a small Secretariat and Working Group, with specific, time-limited Task Forces mandated to lead efforts initially in the fields of vaccine financing (World Bank), advocacy (UNICEF) and country coordination (WHO). In addition, a Global Children's Vaccine Fund will channel funds for vaccines to the neediest countries through its partners and according to given criteria.[1]

[1] Further information may be obtained from: Executive Secretary, Global Alliance for Vaccines and Immunization, c/o UNICEF, Palais des Nations, 1211 Geneva, Switzerland, Tel: +41 22 909 50 20, E-mail: tgodal@unicef.ch.

I.3 Immunization Safety Priority Project

Dr Philippe Duclos presented an overview of the aims and four areas of focus of the Immunization Safety Priority Project, for which a composite workplan of all V&B activities related to immunization safety has been developed. These can be summarized as follows:

- Vaccine Safety

  Proactive attention so that potential risks of new technologies in vaccine development are addressed by the global scientific community and appropriate action taken *(e.g. establish working group on quality/safety of DNA vaccines, make sure safety is a principal end point in trials).*

  Reactive action to ensure a global coordinated response to emerging technical issues to vaccine safety *(e.g. establish a global vaccine safety advisory committee and task force on quality/safety of cell substrates).*

  Routine action to monitor compliance of prequalified vaccines with up-to-date WHO requirements *(e.g. update manufacturing and control information, harmonization of DT antigen content and potency).*

- Research and development of safer/simpler vaccine delivery systems

  Development of safe, thermostable mono-dose vaccine presentations integrated with the injection device *(e.g. develop a sugar-dried vaccine and its delivery systems).*

  Development of vaccines administrated by mucosal routes *(e.g. new aerosol formulations of current measles vaccine).*

  Assessment of slow release technologies.

- Access to safe vaccine delivery systems

  Access to safe sharps disposal and destruction for routine and mass immunization in all countries *(e.g. develop access to systems for disposal and destruction; assess feasibility of thermal melting).*

  Access to safe injection technologies for multi-dose vials by 2002 and for mono-dose presentations by the end of 2002 *(e.g. establish linkages with Safe Injection Global Network (SIGN) and Prevention of Cross Injection Working Group, technical assistance to new manufacturers of auto-disable syringes; harmonize policy; and cost safe injection systems).*

- Identification and management of risks related to immunization

  Establishment of efficient delivery mechanisms to assist countries in managing crisis situations *(e.g. establish Global Advisory Committee on Vaccine Safety; provide technical assistance, particularly to regional offices and countries; review complaints from the field through laboratory support and an AEFI response).*

  Identification of changes to ensure the maintenance of vaccine quality up to delivery and proposal for corrective actions *(e.g. country studies to identify unsafe practices).*

Development of comprehensive resource materials to help EPI managers and national regulatory authorities cope with true or perceived risks *(e.g. produce background documents on rates of AEFIs, develop materials methods; surveillance; update field guide for monitoring AEFIs, web site; support for advocacy work).*

All EPI managers trained in the surveillance and management of adverse events following immunization *(e.g. coordination with international drug monitoring programme; media training; Global Training Network training in AEFI surveillance).*

All national regulatory authorities to have access to a surveillance system for adverse events following immunization.

I.4 Mission of the Immunization Safety Steering Committee

A long discussion took place on how best to realize the mandate of the Committee, the principal objectives of which were presented as follows:

- Review priorities and targets set for the project and propose modifications as appropriate.
- Review and critique strategies that will best achieve the targets and strengthen the capacity of countries and WHO regional offices in all areas related to immunization safety.
- Assess progress against the Immunization Safety workplan, milestones and indicators.
- Advise on the relative balance of focus, resources and activities towards achievement of the various products.
- Provide guidance on specific technical areas as necessary.
- Identify opportunities to enhance the global visibility of, and commitment to immunization safety, including in the area of resources mobilization.
- Explore ways to maximize synergies with other partners involved in immunization safety.
- Advise on the possible contribution of the project to other parts of the Organization.

The Committee will submit an annual report to the Strategic Advisory Group of Experts, through the Director of V&B.

A maximum of ten individual members and an equal number of partner organizations would serve for an initial period of two years. Representation would also be assured from all WHO regions and/or initiatives, with particular attention to developing countries.

Members discussed how their advice and actions could best contribute, both individually and as a collective body, to achieving the aims of the Priority Project, although specific recommendations were deferred to take into account the substantive presentations which were to follow. A synopsis of actions proposed can be found in Part III of this report: conclusions and recommendations.

It was agreed that the full Committee need not meet more than once per year, although smaller focused groups may be formed to examine specific issues. In this respect, a sub-group of the Committee should meet promptly to identify clear and measurable indicators to assist the monitoring and evaluation of the Project.

It was also granted that the Chair and the Secretariat – as well as all members – should be in frequent contact to ensure the timely implementation of the recommendations. It would be important that electronic forms of communication be available for this purpose.

In order to ensure timely and maximum information channels between WHO's advisory groups on vaccination, it had been agreed that some members of the Steering Committee should also serve on the Strategic Advisory Group of Experts (SAGE). Dr Merceline Dahl-Regis was nominated to present the outcome of this first meeting of the Committee to the SAGE the following week.

Moreover, the need for sufficient time to allow for the submission of the annual report of the Steering Committee to SAGE should be taken into consideration when organizing annual meetings of the Committee.

Terms of reference of the Strategic Advisory Group of Experts

The purpose of SAGE is to make recommendations to WHO on all aspects of its vaccine and immunization agenda. In this role, it also serves as principal advisory body for WHO as the lead health agency for policy and strategies in the newly formed Global Alliance for Vaccines and Immunization.

Part II: Summary of presentations and discussions

II.1 Current status of immunization safety activities within V&B teams

Access to Technologies (ATT)

Some of the gaps in immunization safety being addressed by ATT, particularly in the following three areas, were highlighted:

1) Strengthening National Regulatory Authorities (NRAs): Not all countries have access to vaccines of assured quality, quality that is maintained up to administration in the target population. A vaccine of assured quality is that produced in a country where the NRA exercises the six critical control functions identified by WHO, with no unresolved problems reported. To date, 49 have conducted an NRA assessment against indicators, 19 of which now have an institutional development plan to enable them to upgrade their control functions.

2) WHO Global Training Network (GTN): To ensure that NRAs have the appropriate expertise and skills to perform the recommended functions, WHO established in 1996 the Global Training Network to train NRAs and eligible vaccine manufacturers in vaccine regulation. More than 300 staff have been trained in 14 institutions around the world. A new curriculum has been developed to train NRA and EPI focal points on adverse events following immunization. The first course will be launched in November 1999.

3) Safe Injections: The current burden of disease that may be due to unsafe injections emphasizes the need to make injections "safer and simpler". Specific activities include:

   - A joint WHO/UNICEF policy on injection safety, recommending the ultimate sole use in national immunization programmes of auto-disable (AD) syringes.
   - Studies to assess the comparative (internal/external) costs of different injection strategies (disposable, sterilizable and AD) have been performed in three African countries.
   - Testing of needle free injectors in two laboratories indicates potential contamination during injection. Solutions are being sought and a further prototype being tested.
   - Technology transfer: 2 intellectual property owners have agreed to AD production in 4 developing countries that have capacity; others with production potential should follow.

- Following a meeting on safe disposal earlier this year, actions have been initiated to undertake thermo processing tests, to develop needle destroyers, guidelines on waste management at health centres, and a small scale incinerator trial.

Expanded Programme on Immunization (EPI)

A comprehensive summary of the achievements and future objectives of EPI in relation to the immunization safety composite workplan included:

1) Communication channels on potential risks related to immunization: an e-mail network will be developed between immunization programme managers and NRAs to exchange information and questions from countries about adverse events, with the latest technical information.

2) Field guidelines for monitoring and investigating AEFIs as well as managing media crises: a field guide is already published and will be reprinted during 1999.

3) Technical assistance to regional offices and countries for monitoring, investigating and managing AEFI crises including handling media responses and implementing plans of action: an extensive supplement to the field guide on managing AEFIs is in preparation, comprising additional information requested by programme managers – including that on AEFIs during mass campaigns – and a large body of information commissioned during 1999 on the expected background rates of all currently used vaccines. This compendium will be made available in print as well as on the internet.

4) A comprehensive web site "Vaccines are safe" covering all aspects of adverse events can be accessed at http://www.who.int/vaccines-diseases/safety/.

5) Effective detection and reaction mechanisms to assist countries to manage AEFIs and implement quick corrective action, as needed with training: as a global watchdog, V&B staff have been alert to AEFIs around the world, including but not limited to issues such as the potential impact of thiomersal, aluminium and intussusception. As a result of this watchdog role, we have presented WHO's perspective at international meetings and generated action at all levels.

6) Training

   - *Partnership building with the media:* there is an emerging dynamic whereby immunization programme managers are continually under attack from different quarters regarding the safety of immunization. WHO's response has been to design a training workshop, which has been run in two locations with excellent responses. Public communication tools include how to prepare press releases and give press interviews. Participants are interviewed on camera and the video played back and reviewed.
   - *Global Training Network (GTN):* EPI has participated in the development of the GTN as it pertains to AEFIs and will participate in the first training course in November 1999.
   - *Technical assistance:* EPI continues to advise countries experiencing AEFIs, which may include visits to assist the ministry of health. Cooperation with regional offices has also promoted the development of regional guidelines and the mutual gain of expertise.

- *UNICEF vaccines:* producers providing vaccines through the UNICEF tender mechanism must submit package leaflets to UNICEF/WHO for clearance, all of which were reviewed.
- *Reducing programme errors:* EPI is producing information for programme managers on how to reduce programme errors such as toxic shock syndrome following unsafe vaccination techniques.

Quality and Safety of Biologicals (QSB)

Some of the challenges facing QSB in assuring vaccine safety were presented, as well as one mechanism that had recently been established to address questions of vaccine safety.

Recent scientific and technological developments have opened the way to new kinds of products, methods of manufacture and highly sensitive assay procedures. The nature of biologicals, and especially of new vaccines and therapies, raises particular questions regarding standardization and quality control that require consideration at an international level. Questions that arise relate both to efficacy and safety, not only for the individual recipient but possibly for the population at large.

Moreover, as infectious diseases continue to decline, people become more concerned about the risks associated with vaccines. Technological advances have also led to scrutiny of existing vaccines and have sometimes created a climate of concern and criticism. In order to respond promptly and efficiently to vaccine-related adverse event allegations, V&B has established a Global Vaccine Safety Advisory Committee as an independent technical advisory body for reliable scientific assessment on vaccine safety issues through:

- The rigorous review of the latest knowledge, from basic sciences to applied epidemiology, in any particular aspect of vaccine safety of global interest, in collaboration with all parties involved, including experts from industry, national administrations and academia.
- The development and application of causal inferences about the relation of vaccines and/or their components and specific adverse events health outcomes.
- The creation of ad-hoc task forces with the mandate to commission, monitor and evaluate appropriate research on potential association of specific vaccines/components and adverse events.
- This Committee met for the first time in September 1999. In considering its mandate, members underlined the need for the utmost neutrality and integrity in the review of scientific data, and clarity to differentiate between statements issued by WHO or the Committee. The results of the deliberations of the first meeting of this Committee on the causal relationship between alum containing vaccines and macrophagic myofasciitis can be found in the WHO Weekly Epidemiological Record, No. 41, 1999, 74, 337-340.

Vaccine Development (VAD)

The scale of immunization programmes is expected to rise dramatically in the next century as the number of vaccines increases and as mass disease control operations are implemented. With few exceptions, most vaccines are administered as part of routine childhood immunization programmes and thus, unsafe injection practices may inadvertently transmit hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) from one infant to another.

VAD has made considerable efforts to coordinate research on methods by which multi-dose immunization regimens can be reduced to a single dose. Technologies that deliver an antigen in a "programmed way", mimicking a course of conventional vaccines, or that require only one dose to be fully effective, are currently being developed. Microencapsulation aims to entrap in tiny polymeric beads active substances (drugs, hormones, vaccines) that are delivered at different intervals, in a controlled-release fashion.

At the same time, novel drying technologies, which incorporate antigens in inert, temperature-resistant solids, along with progress in the development of injection devices have the potential to change immunization programmes beyond recognition. Finally, immunization via the oral route offers obvious advantages. Only a few vaccines, such as those against polio, cholera or typhoid fever, are licensed for oral administration. However, diverse antigen delivery systems are now being developed using a wide variety of strategies (live vectors, non-living delivery systems, mucosal adjuvants) for administration through mucosal surfaces.

Vaccine Assessment and Monitoring (VAM)

Coordination of the Immunization Safety Priority Project is housed in the Vaccine Assessment and Monitoring team. In line with the immunization safety goals shared with other teams described above, VAM is working to have efficient mechanisms established in all countries to detect serious AEFIs and enable prompt and effective response to minimize negative impacts on health and immunization programmes. Significant contributions have been made, *inter alia*, to training elements related to identifying and managing AEFIs, strengthening surveillance systems and technical assistance at national level, and to the Global Advisory Committee on Vaccine Safety, which first met in September 1999.

Major questions and challenges for the future, which were put to the Committee for reflection, included an analysis of how much surveillance is ideal, to reach which exact level of safety. Criteria and indicators, particularly to assess the quality of AEFI surveillance, and to standardize pre- and post-licensure quality and safety controls, were difficult to define. More collaborative efforts would be undertaken with the International Centre for Drug Monitoring in Uppsala and others to improve the accurate collection and analysis of data on vaccine associated adverse events.

II.2 WHO's role in Immunization Safety: HQ initiatives

Safe Injection Global Network (SIGN)

The Safe Injection Global Network was officially launched in October 1999 at WHO/HQ with the aim of preventing injection-associated bloodborne pathogen transmission through the reduction of injection overuse and ensuring injection safety. This goal should be reached through a broad multidisciplinary behaviour change strategy addressing awareness, provision of supplies, and the setup of a waste disposal infrastructure.

A safe injection does not expose the recipient or the provider to any avoidable risk and does not result in waste that is dangerous for the community. Most medications used in primary care can be administered orally and most vaccines are administered by injections. However therapeutic injections account for 95% of the 12 billion injections administered annually worldwide. These data, along with injection frequency surveys, suggest that injections are overused to administer medications. In developing and transitional countries, many of these injections are unsafe, with an estimated proportion of re-use of injection equipment without sterilization ranging from 15% to 50%.

Epidemiological studies suggest that injection overuse and unsafe injections combine to account for large-scale transmission of bloodborne pathogens worldwide, including hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV. Of these, HBV is the most commonly transmitted agent because of a high prevalence of active infection in the world and a high transmissibility of the virus through percutaneous exposures. Because infections with bloodborne pathogens are initially asymptomatic, particularly in infants, the consequences of unsafe injection practices in immunization programmes cannot be captured by surveillance systems that monitor adverse events following immunization (AEFI) but result in delayed onset of chronic diseases.

The Safe Injection Global Network (SIGN) was constituted as a voluntary association with its secretariat based in the Department of Blood Safety and Clinical Technology at WHO/HQ. SIGN associates include representatives from international organizations and programmes, NGOs, governments, universities, professional organizations, consultants, and industry. SIGN associates agree to collaborate in information exchange, coordination of communication strategies, and development of a common strategic framework. SIGN wants to develop innovative approaches to safe and appropriate use of injections through the acquisition of experience in pilot projects and large-scale introduction of new technologies supporting a safer use of injections. Implementation of policy and plans by countries, donors, and lenders making use of injections are also required.

To monitor the impact of interventions, process indicators reflecting injection frequency and injection safety should be associated to outcome indicators reflecting the incidence of injection-associated infections with bloodborne pathogens and the incidence of injection-related abscesses.

Collaborating Centre for International Drug Monitoring

The WHO Collaborating Centre for International Drug Monitoring, situated in Uppsala, Sweden, was established in 1978 to collate, on a global scale, adverse reactions on both drugs and vaccines. Fifty-six countries contribute to the global database, the main function of which is to generate signals of possible adverse reactions.

In September 1999, WHO convened the Annual Centre's meeting of all national centres participating in the programme. An afternoon session of the meeting was devoted to immunization safety. This session was both collaborative and educational. Recommendations focused on increased collaboration between national Drug Regulatory Authorities, national Pharmacovigilance Centres and national Immunization Programmes. Although there was some controversy as to whether adverse events following immunization should be treated differently from drugs, everyone involved agreed to the importance of accuracy in generating signals and on the specific sensitivity of issuing signals for vaccines.

The educational aspect of the discussions emphasized the need for training of individuals in national Pharmacovigilance Centres and Immunization Programmes.

Working Group on the Prevention of Cross Infection

The Group first met in August 1996 with the remit to review preventive infection procedures, equipment and supplies. The focus and membership of the original group was revitalised in March 1999 with a desire to generate consistent, scientific-based messages from all relevant WHO departments. Indeed, although technical programmes address infection control issues, there is no established generic WHO policy on which to base recommendations, resulting in different messages being given on the same issue. This creates confusion for the "end users" in the field. Such a WHO generic policy on infection control must be based on scientific evidence, or best practices where research is missing, followed by guidelines to help develop comprehensive infection control programmes at country level.

The general objectives of the Working Group on the Prevention of Infection are therefore to reduce morbidity and mortality related to nosocomial infections by increasing the knowledge of infection control concepts among health workers and improve practice in health facilities, as well as developing appropriate policies and regulations.

The work of the cross-cluster group has focused largely in 1999 on supporting the launch of the Safe Injection Global Network, and related issues of blood safety and waste disposal. Opportunities are now being taken to: assess health facilities for ways to reduce cross infection; provide advice to countries to include protective measures when designing health facilities and ensuring appropriate equipment to minimize cross infection; support training of the health care providers and develop indicators to monitor the rate of cross infection at health facilities.

In addition, following a major consultation on "HIV/AIDS and health care personnel: policies and practices" in 1997, WHO is updating as a priority the guidelines on universal precautions.

Inter-Cluster Vaccine Research (IVR) Initiative

WHO has established the Inter-Cluster Vaccine Research (IVR) initiative for the discovery and development of vaccines and vaccination strategies for priority infectious – including parasitic – diseases. This *single* initiative combines activities of common interest and provides opportunities to identify joint projects which deserve high priority or additional resources. Existing line management within clusters will be coupled with inter-cluster *functional* management, based on the "type" of activity, which are grouped as follows:

- Exploratory: promotion and where necessary financing research for candidate vaccines for agreed priority diseases (e.g. malaria, *Shigella* dysentery, etc.), and at new vaccination approaches (e.g. mucosal immunization, needle-free devices).
- Pre-licensure: promotion, coordination and where necessary funding pre-clinical and clinical studies to attain regulatory approval of candidate vaccines.
- Post-licensure: evaluation of new vaccine safety, immunogenicity and efficacy within the context of epidemiological conditions encountered in targeted developing countries; development and assessment of new vaccination strategies.

Strategic evaluation mechanisms at inter-cluster level include an annual scientific and technical review, bimonthly R&D meetings for pre- and post-licensure activities, with human and financial resource management remaining within the existing clusters.

Immunization Safety and Waste Management

The WHO Department for the Protection of the Human Environment described how inadequate management of wastes from immunization may not only compromise the safety of immunizations, but also the safety of other injections, occupational safety or the safety of the community. Waste management should therefore be considered as an integral part of immunization safety, and potential recommendations included:

- Waste management should be put firmly on the agenda of immunization safety, with a specific budget line for related issues, both for development and implementation aspects; the *polluter pays principle* is widely implemented in regulations and industrial practices and should also be (and is in part already) applied to the health care sector.
- When analysing the suitability of immunization techniques or practices, waste management considerations must be included (in addition to injection safety aspects and costs).

Treatment and disposal options for immunization wastes are usually the same as for other health-care activities. Possible recommendations on specific activities of immunization safety could therefore include:

- The development and implementation of waste management options, coordinated through the SIGN network, to ensure that activities are part of the larger efforts needed in this area. Duplication would be avoided and forces joined.

Certain issues of waste management would, however, be specific to immunization (as opposed to injections in general), in particular immunization campaigns, and should be addressed in the framework of immunization safety. Possible recommendations would include:

- Field test disposal options in specific circumstances, such as campaigns, and make available the results.
- Foster the development of immunization methods that minimize waste generation.

II.3 WHO's role in Immunization Safety: regional initiatives

African Region

Dr Tarande of the WHO Regional Office in Harare described three areas related to immunization safety where there was a critical need for improvement, namely vaccine quality, the safety of injections, and monitoring and management of adverse events following immunization.

Vaccine Quality: He explained the difficulties which African nations had faced in assuring the quality of vaccines, many of which did not meet the level required by international standards. This was partly because national regulatory authorities have only recently been able to fulfil vaccine regulatory functions, and partly due to limited laboratory capacity for the monitoring of vaccine quality. In addition, the level of management of vaccine supply and associated resources (needles and syringes) has been poor, with cold chain equipment often in need of replacement.

Safety of Injections: Dr Tarande also reported a high prevalence of unsafe injections in the African Region. More than 70% of countries are still using disposable and/or sterilizable material for immunization, with a prevalence of reuse of disposables and poor sterilization techniques (no time-steam saturation-temperature indicator). Few countries have, or implement, a national policy on the safety of injections.

AFRO therefore planned to support countries in the region in:

- Reducing the use of disposables and sterilizables in favour of auto-disable devices, and has developed a strategy towards sustainability in the funding of ADs (combining government and external financing with lower costs from larger-scale supplies).
- Designing and implementing national policies on the safety of injections.
- Training health workers on the administration of safe injection practices.

Adverse events following immunization (AEFI): Whether or not an adverse event following immunization may be imputed to programmatic error, to the vaccine or to any other reason, AFRO intends to establish a desk for AEFI issues which will enhance efforts to:

- Encourage and support countries to monitor AEFIs in a more systematic way.
- Develop user-friendly and simple data collection instruments for AEFIs.
- Support countries in training EPI managers on monitoring and ways to deal with AEFIs.

Americas/Pan American Health Organization

Drs Castillo and Izurieta from AMRO/PAHO informed participants of the status of immunization safety activities in the Americas, based on recommendations made at the XIIIe meeting of the Technical Advisory Group (TAG).

Immunization safety: PAHO, in collaboration with other agencies, has prepared guidelines for managing immunization safety concerns, which are being made available to all health care workers and EPI managers. The regional office is also promoting the appropriate training of EPI managers, particularly to develop communication skills with the media. Materials are also in development to educate parents about diseases and the known side effects of vaccines they protect against. A third key focus of immunization safety issues is adverse events possibly attributable to vaccination, which should be promptly reported and immediately investigated.

Vaccines of quality: Increased collaboration is being promoted between EPI managers and national regulatory authorities to assure that all vaccines are licensed, fulfil laboratory testing, GMP standards and are subject to post-marketing surveillance.

Safe syringe practices: The only way to ensure that injection equipment is not reused is through the utilization of auto-disable syringes. PAHO therefore supports the dissemination of information to all health care workers on safe injection practices, including on the danger of recapping needles. Moreover, countries using single use disposable syringes must provide the funds for procurement of sufficient syringes and safety boxes, and for supervision to document safe syringe disposal and proper collection/burning of used equipment. PAHO is currently evaluating safe syringe practices in national immunization programmes of the region, and would like to support developmental studies of needle-free injection devices.

Eastern Mediterranean Region

Dr Kamel focused on the priority of the region to increase the capacity of countries to respond effectively to AEFI incidents. Several major recent episodes of AEFIs included the death of 21 infants in Yemen when insulin was given instead of DTP during routine immunization. Similarly in Egypt, public concern focused on five deaths, reported in association with DTP vaccination; and in Jordan, an episode of mass hysteria related to school immunization with Td vaccine resulted in temporary cessation of the routine immunization programme.

As a response to these events, three planning workshops were held in coordination with WHO/HQ attended by the majority of countries in the region. National immunization staff and NRA representatives participated in the workshops as well as the director of surveillance from participating countries. UNICEF staff were also invited. Countries were committed to developing monitoring systems for immunization safety, integrated with existing surveillance activities, and associated with NRAs. The outcomes of the workshops included the development of national plans with the specific objectives of early detection and timely action to rectify any programmatic errors, as well as to address media and public concerns. Forms, data management protocols, feedback procedures and training components were formulated. It was decided to establish expert committees for causality assessments. Indicators were set for monitoring and evaluation. Routine reporting, on a quarterly basis, by Member States to EMRO was also initiated. There are plans to follow-up countries with technical and financial support to ensure implementation of their plans. Two media training workshops were also held, which were considered very successful. An evaluation of the workshops will be made available in due course.

European Region

Dr Colette Roure summarized the situation in the European Region, particularly in the former Soviet republics, of adverse events following immunization, and focused on four major areas: surveillance, safe injection practices, quality assured vaccines and self-sufficiency.

There is increasing public attention in the region – as elsewhere – on vaccine safety issues, which parallels the need for improved surveillance techniques for adverse events, analysis of data and the handling of risk communication.

Safe injections: injections are popular, the majority of which are given outside the health setting. In addition, there is an inadequate supply of needles, syringes, and sterilization facilities. EURO's policy is therefore to work towards a reduction in the number of injections and improve blood safety measures to prevent bloodborne pathogen transmission. This entails training, advocacy, a review of injection practices in selected countries, and guidelines on safe disposal.

Vaccine safety: vaccines must be produced according to the strict procedures and quality standards set by WHO. The European Office is looking to ensure that a national regulatory authority exists for each country and that vaccines are released in accordance with these WHO procedures. To this end, EURO intends to establish and review a database of quality assurance procedures by country, either from a questionnaire, or from an assessment visit.

Self-sufficiency: it is important that all Ministries of Health have a specific budget line to purchase the recommended vaccines – and equipment – for their national immunization programme, without relying on external support.

Adverse events following immunization: an effective disease surveillance and reporting system exists, with national systems to monitor adverse events following immunization. The existing network of high quality laboratory services should be expanded to cover surveillance of other targeted diseases such as measles and pertussis.

South-East Asian Region

All countries in the region currently administer six vaccines (BCG, measles, DTP, DT, TT and OPV). Efforts are being made in some countries to add new vaccines, such as hepatitis B and *Haemophilus influenzae* type b (Hib), to the immunization programme, although this will increase the number of injections per child, and the risk of an unsafe injection.

Two countries procure EPI vaccines through UN agencies together with auto-disable syringes, whereas the other countries procure them directly. Irrespective of the source, all countries have an established national regulatory authority, although many need strengthening.

NRA and NCL staff are being trained through the Global Training Network. Thailand rapidly established an NRA for vaccines as soon as they were aware of its importance.

For the eradication of polio from the region, emphasis and attention has been paid to reaching the unreached (about 10% of children). In a National Immunization Day held in October 1999, 65 infants were erroneously administered "Gentian violet" instead of OPV at one Centre. Adverse reaction following immunization can never be predicted, but the authorities must always be prepared. A sample of the vaccine "intact vials" are usually sent for testing following a reported adverse reaction in the field, although the laboratory does not receive the actual vaccine vial used.

Apart from Bhutan, Maldives and Thailand, all countries use glass syringes and so training in the sterilization of the syringes and its monitoring until a switch over to auto-disable equipment is important. Improved safe disposal mechanisms are also crucial. Training in general is of prime importance, particularly to ensure that acquired knowledge can be transferred to others.

In summary, SEARO perceives the need for:

- Training through the GTN to strengthen NRAs/NCLs in vaccine regulation.
- Policies for safe injections and safe disposal of waste.
- Combination vaccines to reduce the number of injections.

Western Pacific Region

Immunization safety activities in the Western Pacific Region have concentrated on three main areas: injection safety, vaccine quality and the monitoring and management of adverse events following immunization.

The safety of injections, including the proper disposal of used injection equipment, is of primary concern to ensure the well-being of all people. Objectives of regional plan are:

i) To improve safe injection practices in general, whether for vaccines or for any other purpose, and to ensure safe immunization injections in particular in all countries by 2002.

ii) To improve the safe disposal of used injection equipment.

iii) To explore alternative strategies of delivering injections, and disposing of and destroying used injection equipment.

Injection safety must be a concern of both the public and private health sectors. Some countries are currently using reusable equipment; others use disposables; and some are using mixed strategies. National policies to improve the safety of immunization injections are being adopted in an increasing number of countries or provinces in the region.

With regard to the monitoring and management of adverse events following immunization, WPRO has provided technical assistance to EPI programmes and/or NRAs, and to government agencies to promote the development of a monitoring system. Countries that have shown commitment to strengthening their NRA and have earmarked necessary resources have been first to receive technical assistance. Future plans in the region include:

i) Continued support to these countries in their efforts to build an AEFI monitoring system.

ii) The distribution of AEFI guidelines.

iii) A regional workshop with EPI managers and NRA staff.

iv) Support to attend GTN courses on developing an AEFI monitoring system.

v) Introducing AEFI monitoring as part of all measles campaigns in the region.

WPRO has aligned itself with the global strategy for ensuring vaccine quality and uses a similar approach and common technical resources. This has been incorporated in the overall strategy for immunization safety. Activities have focused primarily on the NRAs of three countries, based on government interest and endorsement as well as their vaccine production capabilities. Future regional plans for vaccine quality control and NRA strengthening include continued staff training activities and the provision of technical expertise in these three countries, with increased focus on building the NRA network.

II.4 Consolidating collaboration between Immunization Safety Priority Project and partner organizations

All the partner agencies – or associate members – were invited to comment on their existing activities related to the work plan of the Immunization Safety Priority Project, and which areas could be strengthened. Some of these activities are highlighted below.

Centers for Disease Control and Prevention (CDC)

The Centers for Disease Control and Prevention's (CDC) involvement in immunization safety dates back to the investigation of the inadequately inactivated polio vaccine "Cutter Incident" in 1956 and Guillain-Barré syndrome and "swine flu" vaccine in 1976. Formal surveillance for adverse events following immunizations began in 1978. The redesigned Vaccine Adverse Event Reporting System (VAERS) became operational in 1990 and has recently proven its value in

detecting signal of new vaccine safety concerns (e.g., intussusception after rotavirus vaccine). To test the hypotheses raised by VAERS and other sources, the Vaccine Safety Datalink (VSD) project was created in 1991. The VSD currently links computerized vaccination and medical records on cohort of approximate 6 million (2% US population) in four managed care organizations. The other two major vaccine safety activities at CDC include vaccine risk communications and vaccine development.

The Vaccine Safety and Development Branch at the National Immunization Program serves as the focus for CDC's immunization safety efforts. It has grown during the last decade from a staff of two persons to currently 10 staff (+ 5 trainees) and will likely double in size in the next two years. The CDC is ready and willing to partner with WHO and other parties in ensuring the safety of immunizations worldwide.

United States Agency for International Development (USAID)

The safe delivery of high quality vaccines is an important element of improving the overall quality of health service delivery. Immunization programmes have initiated many of the most progressive efforts to improve the safety of services delivered, although future efforts need to be more integrated. Ensuring that vaccines of known good quality are safely delivered and that associated wastes are safely disposed of, requires efforts in a wide variety of areas. USAID has attempted to work closely with its partners in the areas described below.

USAID has supported WHO's efforts to improve the quality of vaccines used in national immunization programmes for almost ten years. The Global Training Network and initiatives to improve vaccine procurement practices are outstanding examples of WHO's clear vision for the future and a path for getting there.

Support has also targeted technologies to improve safe vaccine delivery, which currently includes: 1) broadening the concept of "bundling" (for injectable contraceptives), 2) facilitating the transfer of technology for the manufacture of AD syringes, 3) supporting the evaluation of UniJect; 4) development and evaluation of devices that will reconstitute lyophilized injectable products as an integral part of the product delivery process, and 5) investigating new methods of stabilizing and delivering vaccines such as "sugar glass" processes.

A recent focus of USAID has been improving the safe disposal of medical wastes, inter alia through: a decision tree to assist decision-makers select appropriate technologies for disposal in a variety of settings; point-of-use needle destroyers adapted for the developing world; evaluation of plasma incinerators for medical wastes; and methods for encapsulating needles to render them safe for general disposal.

USAID is also working with SIGN to: develop standards for the safe delivery of injections; review existing training materials for guidance on the delivery of safe injections (in immunization and family planning programmes); develop a training module for providing safe injections; develop and evaluate with other partners a tool to determine the safety of injection related practices at the country level; and implement a comprehensive demonstration programme in one country to improve the safety all injections.

Although there is growing recognition of the importance of vaccine safety at the international level, in order to ensure sustainability of efforts that will improve safety within countries, vaccine safety must become a priority of national decision-makers. In recognition of this, USAID is disseminating the analyses of perceptions of decision-makers in 38 developing countries regarding injection safety, and will work with SIGN and V&B to integrate the findings of these studies into the design and implementation of a comprehensive advocacy strategy for safe injection.

USAID will continue to support SIGN and the GTN. The development and introduction of new products and technologies will also remain a priority. Special emphasis will be given in the short term to ensuring that VVMs are successfully introduced for all priority vaccines, and that devices that improve the safety of injections and the disposal of medical wastes will be developed, evaluated and introduced. It is currently unclear what role USAID will play in improving vaccine procurement practices. Finally and very importantly USAID believes that special attention must be paid to the development and implementation of an advocacy and communication plan for improving vaccine safety and that the plan must be based on careful analyses of comprehensive empirical data.

United Nations Children's Fund (UNICEF)

Dr Kartoglu described the factors that influence the quality of immunization practices. After a vaccine enters a country there are many human-operated systems that control the handling and use of vaccines. Several joint WHO/UNICEF publications are in print or preparation, including the WHO-UNICEF-UNFPA joint statement on the use of auto-disable syringes in immunization services. In this new joint policy statement,[2] UNICEF reaffirms that its programme funds cannot be used to procure standard disposable syringes for any immunization purpose. UNICEF also announces that as of 1 January 2001, no procurement service contracts (as a service to governments and other organizations) for standard disposable syringes will be entered into. The joint policy states that by the end of 2001, all countries should use only auto-disable syringes or sterilizable syringes for immunization. WHO, UNICEF and UNFPA urge that, by the end of 2003, all countries should use only auto-disable syringes for immunization. All partners of immunization services are requested to finance not only the vaccines, but also safe administration of vaccines, auto-disable syringes and safe management of waste.

Dr Kartoglu further described UNICEF's support to in-service training workshops and "safe immunization practices principles" that will be incorporated into the undergraduate curriculum. A CARK (Central Asian Republics and Kazakhstan) Maternal and Child Health forum has appointed a working group on safe immunization practices with the cooperation of several partners.

[2] See Annex 4.
Also available on the web site: www.who.int/vaccines-documents/DocsPDF99/www9948.pdf

II.5 Advocacy and resource mobilization

The Committee was requested to reflect on the strategies and activities being undertaken to advocate the Project. These included targeted information dissemination, a specific page on the V&B web page, and using all opportunities – particularly relevant international fora — to reinforce messages on immunization safety.

One key activity which will address many of the above is the February 2000 special issue of the WHO Bulletin devoted largely to immunization safety.

Some of the articles discuss what goes into making a vaccine safe. However, since no vaccine – or any other health intervention for that matter – can be 100% safe, other articles look at the new epidemiologic and laboratory tools at our disposal to investigate vaccine safety issues. The roundtable presents a thought-provoking debate on the potential hurdles ahead for vaccination which, hopefully, we can prepare for to ensure that vaccines remain safer than ever.

The editorial is co-authored by the Executive Director of the Health Technology and Pharmaceuticals Cluster and the Leader of the Priority Project. Here, it is explained how the very success of immunization programmes in conquering scourges such as smallpox, poliomyelitis and measles has actually lead to a disproportionate focus on vaccine safety: in the absence of the deadly disease, why take the (albeit minimum) risk of getting vaccinated?

It is expected that this special issue will generate much interest in the safety of immunization, and information materials for the both the public and the media will be prepared to maximize the advocacy opportunity, yet minimize any negative repercussions.

The question of resources mobilization (as opposed to the funding status of the Project) was briefly discussed. It was hoped that the Secretariat would be in a position to raise funds, if necessary, to ensure that all essential activities in the composite work plan were carried out. Of particular importance was the need for contingency seed funds for the Vaccine Safety Advisory Committee, so that any urgent research required could be initiated without delay.

Part III: Conclusions and recommendations

The Steering Committee on Immunization Safety recognized that the goals of vaccine delivery programmes may not be met if there is a lack of trust in the system due to real or perceived safety problems. The local community and the media therefore need to know if there is a problem and how it is being addressed.

Members noted WHO's important leadership role in the area of immunization safety and its responsibility as a champion for the developing world. They were pleased that the new V&B matrix structure allows safety to permeate activities in all V&B teams. The Committee commended the efforts of the Immunization Safety Priority Project as outlined in the V&B 2000-2001 strategic plan to coordinate, communicate, create synergies within the Organization and among partners to maximize the impact of the Project. The participation of many WHO clusters and external partners at the meeting of the Steering Committee is an important element to favour this coordination, which members urged V&B to maintain and enhance, for example the need for close linkages with the WHO press office. Nevertheless, they also cautioned that all WHO departments should harmonize safety messages to avoid conflicting instructions which would negatively affect immunization programmes.

The numerous activities undertaken or planned in the WHO regions, and the important progress accomplished toward improving immunization safety despite limited resources allocated specifically for safety issues, were very encouraging. Moreover, the Committee supported the development of national plans for enhancing programmes for immunization safety.

Members felt that the use of current delivery systems for the wider use of new vaccines in developing countries is of such importance that it should be within the agenda of the Global Alliance for Vaccines and Immunization.

The Steering Committee stressed the importance of:

1) Emphasis on delivery of safe vaccines of high quality, with focus on prevention and safety assurance.
2) Prompt AEFI monitoring and management.
3) Strengthening national regulatory authorities (NRAs).
4) Developing collaboration between NRAs and Immunization (EPI) managers.

The Committee approved in principle the main products/milestones of the proposed V&B strategic plan in relation to immunization safety, and in particular its widely encompassing and proactive focus. Members would like to receive a progress report on the Immunization Safety Priority Project every six months.

III.1 General recommendations

Advocacy

- Strategies must be developed to assure advocacy for vaccine safety and target appropriate levels of government and the health care delivery system (e.g. minister level through the World Health Assembly and the Regional Committees) and not just the EPI/immunization manager. The availability of local data is important to help convince authorities of the need to make immunization safety issues a priority.
- WHO, with key partners, should continue to expand collaboration, communication and coordination, *inter alia* through the compiling of a list of resources, and an information bulletin to assist countries to exchange information on progress toward immunization safety. The Committee considered it important to open a channel of communication between WHO country offices and EPI managers with respect to immunization safety.

National policies

- The concept of the cost of a "safely immunized child", and standards to cost a safely immunized child, should be a composite part of all strategies for financing immunization services, including those under the auspices of the Global Alliance for Vaccines and Immunization (GAVI) partners. These strategies should encompass all costs of the safe delivery of vaccines, including the disposal of residual waste.
- Immunization safety must be emphasized as a core function of immunization systems during health care reform in any political jurisdiction.
- Mass campaigns should be used as an opportunity to promote and improve immunization safety through country capacity building.

Training

- WHO/UNICEF Member States should coordinate and expand access to training as a core element of immunization safety. Such training would include AEFI monitoring, risk communication/media training, injection safety and National Regulatory Authorities functions.
- A training component should be present in the development of any new technology/programme, with emphasis on pre-service training. The integration of the concept of immunization safety into educational establishments for all health professionals and paramedics should be encouraged. Mid level management courses should cover safety and AEFI monitoring, and not just vaccine delivery.

- Relevant partners such as NGOs and private corporations could be solicited to help support training. Programmatic issues such as a high turnover of staff in some countries increase training needs.
- National training plans for NRAs should be developed in all countries.

Monitoring

- A subgroup of the Steering Committee should be formed promptly to identify indicators to monitor progress of the Priority Project, especially for injection safety and AEFI monitoring.
- There is a need for a standard assessment tool of immunization safety for use by national EPI/NRA managers and other stakeholders. Programme assessment tools being developed in particular for use by GAVI and its funding partners, including the World Bank, should include items related to immunization safety.

III.2 Specific recommendations

Assuring vaccine safety

The consistent delivery of safe, quality vaccines – a basic element of the Immunization Safety Priority Project – must be assured from the point of development of the vaccine, through clinical trials to the point of routine use. The strengthening of all NRA functions to ensure this level of safety and quality was considered key to this goal. The Committee further noted that the global policy statement[3] regarding the need to ensure the quality of donated vaccines must be adhered to at national level.

- Up-to-date criteria for the production and quality control of vaccines should be defined, and guidelines and International Reference materials should be developed and made available by WHO to manufacturers and NRAs.
- Pre-clinical and clinical evaluation and standardization of all new technologies ensuring that maximum safety levels are attained should be encouraged by WHO.
- WHO guidelines should be updated on a timely basis to reflect the use of the newest safety administration technologies and methodologies.
- Information on all vaccine components should be included in the WHO publication: "International List on the Availability of Vaccines".[4]

[3] See Annex 5. Also available on the web site www.vaccines.who.int/vaccines-documents

[4] See List of UN prequalified vaccine producers: www.who.int/technology/old_supqual/supqual/unprequalprod.htm

Research and development of safer/simpler vaccine delivery systems

The Steering Committee noted with interest the new technologies that were being explored in the areas of vaccine delivery, although members were not in a position to endorse specific research programmes.

- In principle, safe and effective combination vaccines should be promoted, in part to decrease the number of injections.
- Exploratory seed funding for research and development into cutting-edge technologies with the potential to make immunization programmes safer and simpler should be encouraged within the Intercluster Vaccine Research Initiative as a long-term strategy.
- Recognizing that novel vaccine delivery technologies could have a great impact on safety and simplicity of immunization programmes in the developing world, the Steering Committee recommended that WHO facilitate the independent evaluation and introduction of: (i) delivery systems for parenteral administration which integrates the injection device with the vaccine presentation; and (ii) nasal/oral delivery systems in advanced stages of development, through:
  - Intellectual property assessment.
  - Exploring device/vaccine regulatory issues, including those to ensure the compatibility of devices for the administration of a specific biological.
  - Encouraging the standardization of delivery systems.
  - Development of standards (protocols, devices).
  - Clinical evaluation in appropriate country-settings.
  - Market assessment in developing countries.
  - Training and implementation issues early on in the development cycle.
  - Public-private partnership and financing mechanisms.

The Steering Committee supports the WHO/UNICEF white paper on technologies for vaccine delivery in the twenty-first century that will guide directions for the next ten years.

Access to safe vaccine delivery systems

The Committee sought accelerated efforts to reduce the unacceptable inequalities among regions and countries in their access to safe vaccine delivery systems, and the need to promote the use of vaccines of assured quality, safe injection systems and proper handling of vaccines. In particular, access to auto-disable syringes varies greatly. It also acknowledged that injections related to immunization are only a small fraction of all injections and that V&B is a member of the Safe Injection Global Network, where it coordinates, develops guidelines and sets priorities for immunization injections.

Waste disposal is an immunization safety issue and must be given the attention it deserves:

- Although treatment and disposal options for immunization wastes are usually the same as for other health care activities, particular attention should be given to certain issues relating to disposal which are specific to immunization.
- Disposal options should be field tested, in particular during mass vaccination campaigns, and results made available.
- The development and implementation of disposal options should be coordinated through the SIGN network, to ensure that activities are part of the larger efforts needed in this area which will avoid duplication and prioritize the development of cheaper disposal options.
- The disposal element of the delivery system should be taken into account when analysing the suitability of immunization techniques or practices.
- Foster the development of immunization methods that minimize waste generation (polluter pays principle).

The Committee acknowledged that despite the absence of any one perfect technology, small steps make progress, and each new technology may have something to offer. For access to a safe vaccine delivery system, there is a need to prioritize the short-, medium- and long-term solutions. It is important that all stakeholders collaborate to produce one strong, unified message and with that aim, the Committee applauded the WHO-UNICEF-UNFPA effort to produce a joint statement on the safety of injections.[5]

- National immunization policies should include actions toward safety and waste management (cycle of planning, policy implementation, monitoring) and implementation of these policies should be made accountable.
- Immunization programmes should evaluate/incorporate tools that are currently available to improve safety of vaccine delivery. Once a technology is identified as being safe, improved, and appropriate, a process of rapid introduction into national immunization programmes should be launched where desirable:
  - A clear and strong policy statement/recommendation should be issued by WHO to drive commercialization and the necessary market preparation;
  - Issues of supply/demand, quality assurance, resource allocation and sustainability must be addressed;
  - Recommendations should also take into account solidarity with countries.
- When technology transfer is supported by WHO, all aspects should be considered (IPR, regulatory control, standardization, supply).

[5] See Annex 4. Also available on the web site: www.who.int/vaccines-documents/

Identification and management of risks related to immunization

The Committee stressed the importance of prompt AEFI monitoring and management as a key element of immunization safety and its valuable role to detect programmatic errors and to help face allegations that would be unduly detrimental to immunization programmes. Members were comfortable with the use of the term "AEFI monitoring" to mean surveillance. However, since AEFI monitoring is but one mechanism to achieve the larger goal of immunization safety, a general preference was proposed to describe the overall endeavour as "immunization safety monitoring", which has a more positive connotation for the general public than the narrower (and negative sounding) "adverse events". EPI managers and NRAs must also be able to report on vaccine safety issues freely and to address any structural/organizational issue that would be a deterrent to the transparency and prompt management of such issues.

The Committee also recognized the limited capacity of many countries to deal with these issues. The Committee supports the concept of minimum standards (set of reportable conditions) for AEFI monitoring compatible with the current guidelines on monitoring of AEFI and intended for EPI managers.

They also underscored the fundamental differences between vaccines and drugs with respect to causality assessment and monitoring that have to be properly taken into account. In many countries EPI managers are involved with AEFI monitoring and this should be taken into account when meeting of the participating centres of the International Drug Monitoring Programme are being organized.

It was recognized that media training is critical in helping countries properly face allegations. Risk communications/media training must therefore be one of the priorities for EPI managers during their regular meetings. Current HQ and regional efforts to strengthen collaboration between NRAs and EPI managers were considered vital, along with the need for training materials.

The Committee applauded the creation of the Global Advisory Committee for Vaccine Safety as an important and key element to properly and promptly deal with potential safety issues. Members agreed with the need for the Advisory Committee to review safety issues based on best scientific evidence in an independent and unbiased manner.

In summary:

- The capacity for early detection, proper response and timely management of vaccine safety concerns, particularly to correct programmatic errors, should be strengthened. Although the process may vary between regions, they must have capacity to achieve these objectives The development of a national plan of immunization safety should include this as one of its goals.
- When dealing with AEFIs, national authorities should have access to science-based information and involve NRAs.
- Current activities such as the Global Training Network curriculum on AEFI should be encouraged and further expanded.
- The Uppsala International Drug Monitoring Centre training on adverse events monitoring should be used to maximize synergies with the international drug monitoring programme to educate members on specific issues related to AEFI monitoring and causality assessment.

Annex 1:

Programme

Monday, 25 October 1999

Morning — Opening session

Opening remarks
Michael Scholtz, Executive Director, Health Technology and Pharmaceuticals

Overview of Department of Vaccines and Biologicals and the Global Alliance for Vaccines and Immunization
Maureen Birmingham, Coordinator, Vaccine Assessment and Monitoring

Presentation of Immunization Safety Priority Project
Philippe Duclos, Project Leader

Mission of the Immunization Safety Steering Committee
Maureen Birmingham

Terms of Reference

Interaction with the Strategic Advisory Group of Experts (SAGE)

Discussion

Expected outcome:

Adoption of terms of reference and modus operandi

Overview of immunization safety composite work plan

Current status of products and resources – presentation by V&B teams

- Access to Technologies, *Lahouari Belgharbi*
- Expanded Programme on Immunization, *John Clements*
- Quality Assurance and Safety of Biologicals, *Luis Jodar*
- Vaccine Development, *Luis Jodar*
- Vaccine Assessment and Monitoring, *Philippe Duclos*

Monday, 25 October 1999 (cont.)

General discussion on team presentations, and how to measure and evaluate the impact of the Priority Project

Expected outcomes

- Review priorities and targets and propose modifications as appropriate.
- Assessment of achievements.
- Recommendations on composite work plan: relative balance of focus, resources and activities towards achievements of the various products.
- Identification of indicators and milestones.

Afternoon WHO's proactive and reactive capability in immunization safety (*discussion facilitated by Philippe Duclos)*

Consolidating collaboration between Immunization Safety Project and:

- Safe Injection Global Network (SIGN) Project, *Yvan Hutin.*
- Prevention of Cross Infection Working Group, *Naeema Al-Gasseer.*
- Intercluster Vaccine Research, *Howard Engers.*
- Collaborating Centre for International Drug Monitoring, *Mary Couper.*
- Protection of the Human Environment, *Annette Pruess.*

Consolidating collaboration with WHO regions:

Africa

Americas

Eastern Mediterranean

Europe

South-East Asia

Western Pacific

Expected outcomes

- Discussion and agreement on WHO's comparative advantages.
- Steering Committee appraised of WHO-wide activities.
- Review of internal collaborative mechanisms and identification of gaps.
- Recommendations on strategies to achieve the targets and strengthen the capacity of countries and WHO regional offices.

Tuesday, 26 October 1999

Morning — Consolidating collaboration between Immunization Safety Priority Project and partner organizations

Insights from partners followed by open discussion

Identification of gaps and commitment of partners to specific areas of activity

Expected outcome

- Recommendations for strengthening external partnerships and maximize synergies with all partners.

Afternoon — Future activities: How to advocate a spirit of safety

Advocacy for safety: information dissemination, web page, international fora, special thematic issue of WHO Bulletin (Feb 2000), etc.

Management and resource mobilization

Expected outcome

- Agreement on strategies for sustaining momentum, target audiences, and resources.

Review of recommendations of the Steering Committee

Expected outcome

- Agreement on report of recommendations to SAGE.

Closing Session (*Chair)*

Annex 2:

List of participants

Members

Dr Merceline Dahl-Regis, Chief Medical Officer, Ministry of Health, P.O. Box N3730, Nassau, New Providence IS, Bahamas
Tel: +1 242 322 74 73, Fax: +1 242 322 77 88
E-mail: mdr@batelnet.bs

Dr Ahmed A. Darwish, EPI Manager, c/o WR, Ministry of Health and Population, P.O. Box 146, Cairo 11516, Egypt
Tel: +20 594 1779 (205730270h), Mobile: 0123 112141, Fax: +202 355 3756
E-mail: darmoh@hotmail.com

Dr M. Carolyn Hardegree, (Chairperson) 8808 Tallyho Trail, Potomac, MD 20854, USA
Tel: +1 301 299 5403, Fax: +1 301 299 6318
E-mail: jsdchd@aol.com

Dr Alenka Kraigher, Epidemiologist, Institute of Public Health, National Coordinator for Communicable Diseases and EPI, Trubarjeva 2, 1000 Ljubljana, Slovenia
Tel/Fax: +386 61 323 940
E-mail: alenka.kraigher@gov.si / alenka.kraigher@ivz.sigov.mail.si

Dr Elizabeth Miller, Head, Immunization Division, Public Health Laboratory Service, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK
Tel: +44 181 200 68 68 x 4430, Fax: +44 181 200 7868
E-mail: emiller@phls.nhs.uk

Mrs Mavis P. Nxumalo, Programme Manager, Swaziland Expanded Programme on Immunization, Ministry of Health, c/o Public Health Unit, P.O. Box 1119, Mbabane, Swaziland
Tel: +268 4045166 (h), Fax: +268 4040746
E-mail: epiari@realnet.co.sz

Mr Greg Sam, (Rapporteur), Director, Immunization, National Centre for Disease Control, Commonwealth Department of Health and Family Services, Bowes Street, Canberra, ACT 2614, Australia
Tel: +61 2 6289 6859, Fax: +61 2 6289 8098
E-mail: greg.sam@health.gov.au

Dr Lucky S. Slamet, Head, Sub-Directorate of Drug Registration, Directorate-General of Drug and Food Control, Ministry of Health, Jalan Percetakan Negara No. 23, Jakarta 10560, Indonesia
Tel: +62 21 424 4755, ext. 103, Fax: +62 21 426 5927
E-mail: regobpom@indo.net.id

Dr Yu Jing Jin, Director, Division of Vaccine Preventable Diseases, Department of Disease Control, Ministry of Health, Beijing, China
Tel: +8610 6879 2514, Fax: +8610 403 3122
E-mail: ddcyjj@public3.bta.net.cn

Associate Members

Dr Robert T. Chen, MS-E-61, Chief, Vaccine Safety & Development Activity, National Immunization Program, Centers for Disease Control & Prevention (CDC), 1600 Clifton Road, NE, Atlanta, GA 30333, USA
Tel: +1 404 639 8256, Fax: +1 404 639 8834
E-mail: rtcl@cdc.gov

Dr Yves Bergevin, Senior Health Specialist, Policy Branch, Canadian International Development Agency (CIDA), 200 Promenade du Portage, Hull, Quebec, K1A 0G4, Canada
Tel: + 1 819 997 7870, Fax: +1 819 997 9049
Email: yves_bergevin@acdi-cida.gc.ca (unable to attend)

Dr John Lloyd (representing Dr Mark Kane), Bill and Melinda Gates Children's Vaccine Program (CVP), c/o PATH, 4 Nickerson Street, Seattle, WA 98109, USA
Tel: +1 206 285 3500, Fax: + 1 206 285 6619
E-mail: mkane@path.org

Dr Tore Godal, Executive Secretary, Global Alliance for Vaccines and Immunization (GAVI), c/o UNICEF, Palais des Nations, 1211 Geneva 10, Switzerland
Tel: +4122 909 5020, Fax: +41 22 909 5900
E-mail: tgodal@unicef.ch (unable to attend)

Dr Robert Sharrar, International Federation of Pharmaceutical Manufacturers Association (IFPMA), Senior Director, Vaccine Safety, Worldwide Product Safety and Epidemiology, Merck & Co., Inc., P.O. Box 4, BLB-30, West Point, PA 19486, USA
Tel: + 1 610 397 2868, Fax: +1 610 397 7916
E-mail: sharrar@merck.com

Dr Bradley Hersh, Medical Officer, International Federation of the Red Cross (IFRC), 17 ch. des Crêts, B.P. 372, 1211 Geneva 19, Switzerland
Tel: +41 22 730 4340, Fax: +41 22 733 0395
E-mail: hersh@ifrc.org

Mr Akira Nishimoto, Planning Division, Medical Cooperation Department, Japan International Cooperation Agency (JICA), Shinkuju Maynds Tower Building, 8th Floor, 1-1, Yoyogi, 2-Chome, Shibuya-ku, Tokyo 151-8558, Japan
Fax: +813 5352 5277

Dr Nobuhiko Okabe, Chief, Division of Surveillance and Information, Infectious Disease Surveillance Center, National Institute of Infectious Diseases, 1-23-1 Toyama, Shinjuku, Tokyo 162 8640, Japan
Tel: +813 5285 1268, Fax: +813 5285 1129
E-mail: okabenob@nih.go.jp

Dr Melinda Moree, Program for Appropriate Technology in Health (PATH), 4 Nickerson Street, Seattle WA 98109, USA
Tel: +1 206 285 3500, Fax: +1 206 285-6619
E-mail: mmoree@path.org

Dr Umit Kartoglu, Health Officer, United Nations Children's Fund (UNICEF), 15 Republican Square, 6th Floor, Almaty 480013, Kazakhstan
Tel: +7 3272 684757, Fax: +7 3272 501662
E-mail: ukartoglu@unicef.org

Mr Stephen Landry, Children's Vaccine Program, Office of Health and Nutrition, United States Agency for International Development (USAID), Ronald Reagan Building, Washington, D.C. 20528-3700, USA
Tel: +1 202 712 4808, Fax: + 1 202 216 3702
E-mail: slandry@usaid.gov

WHO Secretariat

Regional Offices

Dr Tarande Manzila, New Vaccines Officer, World Health Organization, Regional Office for Africa (AFRO), Medical School, C. Ward, Parirenyatwa Hospital, Mazoe Street, P.O. Box BE 773, Belvedere, Harare, Zimbabwe
Tel: +1 407 733 9157, Fax: +1 407 733 9000
E-mail: manzilat@whoafr.org

Dr Carlos Castillo, Epidemiologist, Division of Vaccines and Immunization (HVP), World Health Organization, Regional Office for the Americas/ Pan American Health Organization (AMRO/PAHO), 525, 23rd Street N.W., Washington, D.C. 20037, USA
Tel: +1 202 974 3269, Fax: +1 202 974 3635
E-mail: castilsc@paho.org

Dr Héctor Izurieta, Epidemiologist, Division of Vaccines and Immunization (HVP), World Health Organization, Regional Office for the Americas/ Pan American Health Organization (AMRO/PAHO), 525, 23rd Street N.W., Washington, D.C. 20037, USA
Tel: +1 202 974 3000, Fax: +1 202 974 3663
E-mail: izurieth@paho.org

Dr Taky Gaafar, Regional Adviser, Vaccine-Preventable Diseases and Immunization, World Health Organization, Regional Office for the Eastern Mediterranean (EMRO), P.O. Box 1517, Alexandria 21511, Egypt
Tel and Fax: +203 4833 285
E-mail: gaafart@who.sci.eg

Dr Faten Kamel, Medical Officer, Vaccine-Preventable Diseases and Immunization, World Health Organization, Regional Office for the Eastern Mediterranean (EMRO), P.O. Box 1517, Alexandria 21511, Egypt
Tel and Fax: +203 4833 285
E-mail: kamelf@who.sci.eg

Dr Colette Roure, Regional Adviser, Expanded Programme on Immunization (EPI), World Health Organization, Regional Office for Europe (EURO), 8 Scherfigsvej, 2100 Copenhagen, Denmark
Tel: +45 39 171534, Fax: +45 39 171818
E-mail: cro@who.dk

Dr Jaspal Sokhey, Medical Officer, Vaccine Safety and Quality, World Health Organization, Regional Office for South-East Asia (SEARO), World Health House, Indraprastha Estate, Mahatma Gandhi Road, New-Delhi 110002, India
Tel: +91 172 573782
E-mail: sokheyj@whosea.org

Dr Yoshikuni Sato, Medical Officer, Expanded Programme on Immunization, World Health Organization, Regional Office for the Western Pacific (WPRO), P.O. Box 2032, Manila 1000, Philippines
Tel: +632 528 9971, Fax: 632 521 1036
E-mail: satoy@who.org.ph

WHO headquarters
Avenue Appia, 1211 Geneva, Switzerland
Tel: +41 22 791 1111

Dr Michael Scholtz, Executive Director, HTP
Tel: 791 4798, E-mail: scholtzm@who.int

Dr Teresa Aguado, Acting Coordinator, Vaccine Development, V&B/HTP
Tel: 791 2644, E-mail: aguadom@who.int

Dr Naeema Al-Gasseer, Organization of Health Services Delivery, EIP
Tel: 791 2325, E-mail: algasseern@who.int

Dr Bruce Aylward, Medical Officer, Expanded Programme on Immunization, V&B/HTP
Tel: 791 4419, E-mail: aylwardb@who.int

Dr Lahouari Belgharbi, Technical Officer, Access to Technologies, V&B/HTP
Tel: 791 3925, E-mail belgharbil@who.int

Dr Maureen Birmingham, Coordinator, Vaccine Assessment and Monitoring, V&B/HTP
Tel: 791 4359, E-mail: birminghamm@who.int

Ms Kay Bond, Administrator, Immunization Safety Priority Project, V&B/HTP
Tel: 791 2262, E-mail: bondk@who.int

Dr John Clements, Medical Officer, Expanded Programme on Immunization, V&B/HTP
Tel: 791 4402, E-mail: clementscj@who.int

Dr Mary Couper, Medical Officer, Quality Assurance and Safety: Medicines, EDM/HTP
Tel: 791 3643, E-mail couperm@who.int

Dr Nora Dellepiane, Scientist, Access to Technologies, V&B/HTP
Tel: 791 4788, E-mail: dellepianen@who.int

Dr Philippe Duclos, Medical Officer, Vaccine Assessment and Monitoring, and Immunization Safety Priority Project Leader, V&B/HTP
Tel: 791 4527, E-mail: duclosp@who.int

Dr Jean Emmanuel, Director, BCT/HTP
Tel: 791 4387, E-mail: emmanuelj@who.int

Dr Howard Engers, Intercluster Vaccine Research Initiative, Communicable Disease Research and Development
Tel: 791 3736, E-mail: engersh@who.int

Dr Yvan Hutin, Medical Officer, SIGN Coordinator, BCT/HTP
Tel: 791 3431, E-mail: hutiny@who.int

Dr Luis Jodar, Scientist, Vaccine Development, V&B/HTP
Tel: 791 3744, E-mail: jodarl@who.int

Ms Ulla Kou, Associate Professional Officer, Vaccine Assessment and Monitoring, V&B/HTP
Tel: 791 4289, E-mail: kouu@who.int

Dr Julie Milstien, Acting Coordinator, Access to Technologies, V&B/HTP
Tel: 791 3564 E-mail: milstienj@who.int

Mr Chris Nelson, Scientist, Vaccine Assessment and Monitoring, V&B/HTP
Tel: 791 3615, E-mail: nelsonc@who.int

Dr Annette Pruess, Water, Sanitation and Health, Department of Protection of the Human Environment, SDE
Tel: 791 3584, E-mail: pruessa@who.int

Dr Jonathan Quick, Director, EDM/HTP
Tel: 791 4443, quickj@who.int

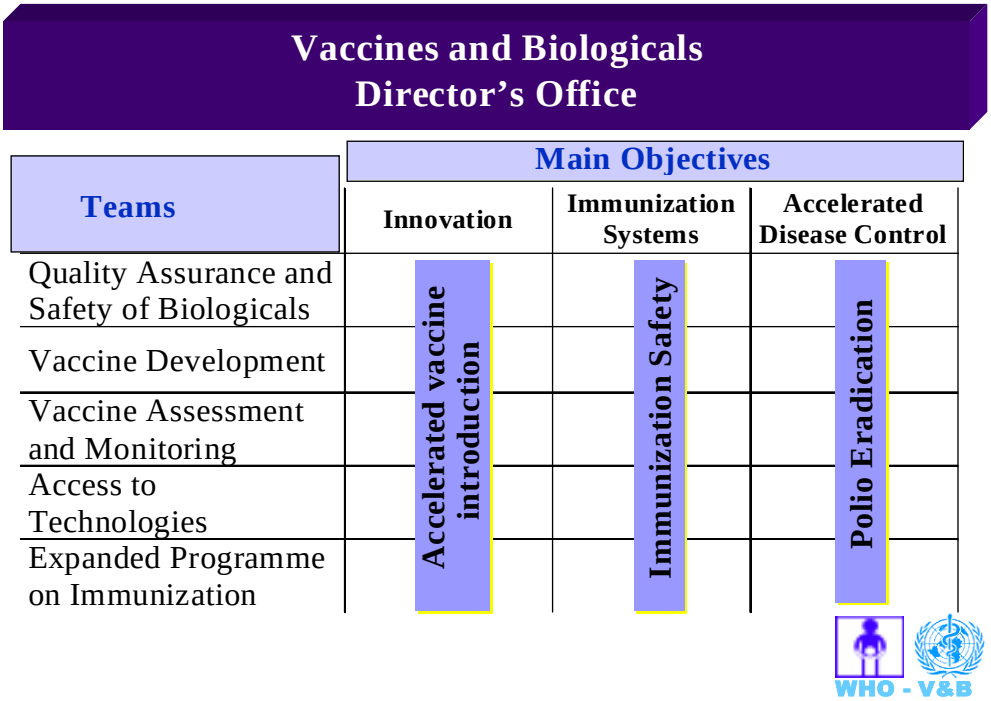
Dr Jay Wenger, Medical Officer, Expanded Programme on Immunization, V&B/HTP
Tel: 791 4511, E-mail: wengerj@who.int

Dr Roy Widdus, Coordinator, Children's Vaccine Initiative
Tel: 791 4369, E-mail: widdusr@who.int

Mr Michel Zaffran, Programme Manager, V&B/HTP
Tel: 791 4373, E-mail: zaffranm@who.int

Annex 3:

Structure of WHO Department of Vaccines and Biologicals



Annex 4:
Safety of injections

WHO-UNICEF-UNFPA
Joint Statement on the Use of Auto-Disable Syringes in Immunization Services

1. The reuse of standard single-use disposable syringes[1] and needles places the general public at high risk of disease and death.

2. The auto-disable syringe, which is now widely available at low cost, presents the lowest risk of person-to-person transmission of bloodborne pathogens (such as Hepatitis B or HIV) because it cannot be reused. The auto-disable syringe is the equipment of choice for administering vaccines, both in routine immunization and mass campaigns.

3. "Safety boxes", puncture-proof containers - for the collection and disposal of used disposable and auto-disable syringes, needles and other injection materials - reduce the risk posed to health staff and the general public by contaminated needles and syringes.

4.
   - WHO, UNICEF and UNFPA reaffirm the current policy that auto-disable syringes, vaccines and safety boxes should continue to be supplied as a "bundle" *(see box, page 4)* for all elective and emergency campaigns.
   - UNICEF reaffirms its current policy that UNICEF programme funds cannot be used to procure standard disposable syringes for any immunization purpose.
   - UNICEF announces that, as of 1 January 2001, no procurement service contracts[2] for standard disposable syringes will be entered into.
   - WHO, UNICEF and UNFPA urge that, by the end of 2001, all countries should use only auto-disable syringes or syringes which are designed to be sterilized. Standard disposable syringes should no longer be used for immunization.
   - WHO, UNICEF and UNFPA urge that, by the end of 2003, all countries should use only auto-disable syringes for immunization.

5. All partners of immunization services are requested to finance not only the vaccines, but also the safe administration of vaccines, auto-disable syringes and safe management of waste. Partners should do this by planning and implementing the above strategy, as well as by supporting related training, supervision and sensitization activities.

Background

Information reaching WHO, UNICEF and UNFPA consistently highlights the widespread occurrence of unsterile injection practices and identifies a major cause as insufficient supplies of syringes and needles[3]. Unsafe injections can result in the transmission of bloodborne pathogens from patient-to-patient, patient-to-health worker and, more rarely, health worker-to-patient. The community at large is also at risk when injection equipment is used and then not safely disposed of. In many instances, used equipment is reused, sold or recycled because of its commercial value. The imperative to improve safety of injections in immunization services is underlined by the publication of articles in the *WHO Bulletin* (October 1999) which show that, although immunization injections are thought to be safer than curative injections, around 30% of immunization injections are still unsafe. Much evidence of reuse of disposable syringes exists and even recent country reviews suggest that sterilization of syringes and maintenance of sterilization equipment is not systematic.

Last year, in the developing world, routine immunization of children under one year and immunization of women of childbearing age with tetanus toxoid (TT) accounted for over one billion injections. In addition to routine immunizations, measles control/elimination activities and disease-outbreak control operations together delivered more than 200 million injections in the same year.

Hepatitis vaccine is now in use in half of the developing countries and Hib, measles-mumps-rubella (MMR) and pentavalent vaccines are already widely used in the Americas. Acceleration of special activities which aim at the elimination of maternal and neonatal tetanus and at better control of measles has begun. And a Global Alliance of Partners of Immunization Services (GAVI) is being formed to assure access to new vaccines for many of the poorest countries where the vaccines are needed most.

These increases of immunization services, including the elimination and control campaigns, offer an opportunity for improvement and make it imperative that injections are made safe for people.

The disease burden associated with unsafe injection practices has been estimated[4] and the cost implications of treatment of these diseases has been quantified[5]. Each unsafe injection costs governments between three to five times the extra cost of auto-disable syringes (which guarantee a sterile injection), not to mention the toll in terms of human suffering.

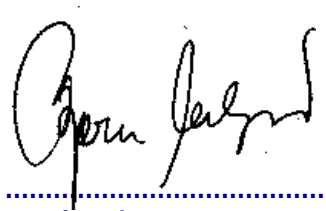
Strategy

Over the past years, WHO, UNICEF and UNFPA have launched a number of initiatives which aim to improve the safety of injections. The most recent was the precursor to this joint statement in 1997[6] which related to the use of auto-disable syringes and safety boxes in immunization campaigns. That policy has assured the simultaneous budgeting and parallel purchasing and shipping of sufficient syringes and safety boxes for each consignment of vaccines for mass campaigns. Now, with a broad experience of the use of this equipment in the field, is the time to consolidate a policy to cover all administration of vaccine.

WHO and UNICEF have agreed to implement a strategy to ensure that special attention is paid to the safe administration of vaccines, both in routine immunization services and during mass campaigns. The policy statement *(on page 1)* defines the position of WHO and UNICEF and is intended as a guide to other partners of immunization services, including national ministries of health.

In addition to this policy statement, WHO and UNICEF recommend that:

- Countries exert maximum effort to ensure that procedures for injection safety are rigorous -this includes routine use and monitoring of indicators of sterilization while sterilizable equipment is still used. Partner agencies involved in immunization programmes in countries should provide maximum support for the strengthening of safe injection practices.
- Urgent attention be given to develop appropriate tools (current monitoring tools are still insufficient to objectively demonstrate compliance to safe injection practices).
- Agencies supporting immunization services be encouraged to provide time-limited financial support to countries procuring standard disposable syringes for immunization until government-won budgets can be increased to cover the additional cost of auto-disable syringes.
- Agencies supporting immunization services which fund the purchase of locally-manufactured standard disposable syringes for immunization should assist countries with technology transfer to enable them to switch to auto-disable syringes in the shortest possible time.
- Used auto-disable syringes should be deposited in safety boxes without re-capping, burned locally and the remains buried underground - until improved disposal methods are developed. Urgent attention should be given to develop improved means for effective, safe and environmentally-acceptable waste processing and final disposal of auto-disable syringes.



B. Melgaard
Director, Vaccines & Biologicals
World Health Organization

V. Li-Frankenstein
Director, UNICEF Supply Division
United Nations Children's Fund,
Copenhagen

S. Rasheed
Director, UNICEF Programme Division
United Nations Children's Fund,
New York

M. Nizamuddin
Director, Technical and Policy Division
United Nations Population Fund

Ibrahim Osman
Under Secretary General, National Society,
Cooperation and Development (NSCD),
International Federation of Red Cross
& Red Crescent Societies

FOOTNOTES

[1] Auto-disable (A-D) syringes conform to the WHO/V&B Performance Specifications E8/DS1 and DS2 and include pre-filled pouch-and-needle injection devices. This statement applies only to available supplies of A-D syringes.

[2] UNICEF procurement service contracts cover the procurement of supplies and equipment by UNICEF as a service to governments and other organizations.

[3] Review: Unsafe injections in the developing world and transmission of bloodborne pathogens, Simonsen L (Ph.D.), Kane A, Lloyd J, Zaffran M, Kane M (M.D.), *WHO Bulletin* October 1999.

[4] Unsafe injections in the developing world: Region based estimates of the transmission of bloodborne pathogens, Kane A et al. *WHO Bulletin* October 1999.

[5] Direct and indirect costs of alternative injection technologies used in immunization services, Ekwueme et al. (Unpublished study with WHO, October 1999.)

[6] Safety of Injections: WHO-UNICEF policy statement for mass immunization campaigns, WHO/EPI/LHIS/7.04 Rev.1 – replaced by this statement, WHO/V&B/99.25.

The term "bundling" has been chosen to define the concept of a theoretical "bundle" which must comprise each of the following items:

- Good quality vaccines
- Auto-disable syringes
- Safety boxes

The implication is that none of the component items can be considered alone; each component must be considered as part of a "bundle" which contains the other two. "Bundling" has no physical connotation and does not imply that items must be "packaged" together.

WHO/VSQ/97.05
ORIGINAL: ENGLISH
DISTR.: GENERAL

GPV POLICY STATEMENT

Vaccine donations

Introduction

A vaccine donation is defined as a shipment of vaccine for which a government does not pay. Properly managed, vaccine donations may be useful to immunization programmes. However, accepting a vaccine donation could leave a country vulnerable to problems. For example, if there is no control over the specifications of the vaccine, or if the donated vaccine does not meet the needs of the government's immunization programme, the donation could actually disrupt the programme.

The aim of these guidelines is to improve the management of donated vaccines, and not to hinder donations. Vaccines shipped through UNICEF Supply in Copenhagen may technically be considered as donations, but as their specifications are developed by a collaborative effort between country officials and UNICEF country staff, such vaccines are not included in these guidelines.

The need for a policy on vaccine donations

The benefits of vaccine donations cannot be over-emphasized. There are many different reasons for vaccine donations. These include emergencies, such as disease outbreaks, or sudden shortages of stock during supplementary immunization activities, corporate donations, bilateral aid, or assistance in cases where the entire health infrastructure has been put at risk, such as during conditions of armed combat. Although these scenarios differ, there are some basic principles which should be considered whenever a donation is to be made which will ensure the optimization of the benefits of the donated vaccines for both the donor and the recipient. These guidelines aim to describe the approach of Good Donation Practice on the part of both donor and recipient.

While vaccine donations are designed to benefit the recipient, they do not always achieve this. Some examples are given below of situations where donations actually harmed the recipient country immunization programme.

Global Programme for Vaccines and Immunization
Vaccine Supply and Quality • World Health Organization
1211 Geneva 27
Fax: 022 791 4193; E-mail: gpv@who.ch

In one country counterfeit meningitis vaccine was donated by a neighboring country at the peak of a meningitis outbreak. The counterfeit vaccine was ineffective at best, and at worst caused harm to the recipient. In either case, public confidence in the immunization programme was threatened.

BCG vaccine with no remaining shelf life was donated to an African country by an nongovernmental organization. Vaccines donated which are at the end of their shelf life generally cannot be used. If they are sent to immunization centers, staff will either have to ignore their training which tells them to follow the expiration date, or not use the vaccine. The result either undermines training and good immunization practices or a large amount of vaccine must be destroyed.

A large donation of OPV suffered a cold chain break in transport. In this case, the vaccine was donated at the request of WHO, by a manufacturer for a polio National Immunization Day. In this particular case, normal precautions had not been taken to guard the potency of the vaccine throughout transport to the recipient country. The result was that the cold chain was broken, the vaccine could not be used, and the NID had to be postponed.

Needed infrastructure

Most recipients of vaccine donations are countries dependent on UNICEF and other donors for their supply of vaccines. Many lack infrastructure to handle donations adequately. WHO recommends that all countries, including those which receive all their vaccines from UNICEF, exercise at least two essential national control functions: a published set of requirements for licensing, and surveillance of vaccine field performance (monitoring of adverse events following immunization). In the case of a problem in the field which may be vaccine related, or of doubt of vaccine potency because of a cold chain break in transport, UNICEF can be notified and, if vaccine testing is needed, WHO laboratories can be used.

But countries still have a responsibility to develop these two basic systems. To date, of 88 countries dependent on UNICEF for their vaccines, only 12 are assuring these two functions.

WHO drugs donations guideline

All countries which are likely to receive donated vaccine need a policy on donations. WHO has already published guidelines for receipt of donations of drugs (WHO/DAP/96.2). These are based on four core principles:

(1) Maximum benefit to the recipient;
(2) Respect for wishes and authority of the recipient;
(3) No double standards in quality; and
(4) Effective communication between donor and recipient.

These four principles have been expanded into 12 guidelines that apply to vaccines as well as pharmaceuticals.

1. All drug donations should be based on an expressed need and be relevant to the disease pattern in the recipient country. Drugs should not be sent without prior consent by the recipient.

2. All donated drugs or their generic equivalents should be approved for use in the recipient country and appear on the national list of essential drugs, or, if a national list is not available, on the WHO Model List of Essential Drugs, unless specifically requested otherwise by the recipient.

3. The presentation, strength, and formulation of donated drugs should, as much as possible, be similar to those commonly used in the recipient country.

4. All donated drugs should be obtained from a reliable source and comply with quality standards in both donor and recipient country. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce should be used.

5. No drugs should be donated that have been issued to patients and then returned to a pharmacy or elsewhere, or were given to health professionals as free samples.

6. After arrival in the recipient country all donated drugs should have a remaining shelf life of at least one year.

7. All drugs should be labelled in a language that is easily understood by health professionals in the recipient country; the label on each individual container should at least contain the International Nonproprietary Name, batch number, dosage form, strength,, name of manufacturer, quantity in the container, storage conditions, and expiry date.

8. As much as possible, donated drugs should be presented in larger quantity units and hospital packs.

9. All drug donations should be packed in accordance with international shipping regulations, and be accompanied by a detailed packing list which specifies the contents of each numbered carton by INN, dosage form, quantity, batch number, expiry date, volume, weight, and any special storage conditions. The weight per carton should not exceed 50 kilograms. Drugs should not be mixed with other supplies in the same carton.

10. Recipients should be informed of all drug donations that are being considered, prepared, or actually underway.

11. In the recipient country the declared value of a drug donation should be based upon the wholesale price of its generic equivalent in the recipient country, or, if such information is not available, on the wholesale world-market price for its generic equivalent.

12. Costs of international and local transport, warehousing, port clearance and appropriate storage and handling should be paid by the donor agency, unless specifically agreed otherwise with the recipient in advance.

Application to vaccine donations

For the most part, these guidelines are applicable for vaccines as well. Four proposed minimum specifications for vaccine donations restate these guidelines in a manner applicable to vaccines:

- the vaccine is helpful to the immunization programme; that is, the donated vaccines are consistent with the goals of the immunization programme;

- the vaccine is subject to prescribed licensing and control procedures set up by the recipient government;

- the vaccine meets all specifications consistent with other vaccines in the programme, including potency, liquid or freeze-dried presentation, transport, shelf life, number of doses per vial, thermostability, and labeling;

- the vaccine should be shipped only on request of the responsible national officials.

Policy implementation

Implementation of the policy will require some infrastructure within the country. However, the needs are not essentially different from those already identified as basic national control functions. There is a need for a focal point to check vaccines upon receipt and the ability to refuse vaccine donations not meeting the criteria. This implies a need for criteria, such as a published set of requirements for licensing, and their application. There is also a need for a system to detect and investigate complaints from the field, essentially the second critical control function, surveillance of vaccine field performance. Thus, developing a vaccine donations policy will reinforce the need for and functioning of the basic components of a national control system for vaccines.

WHO, through its headquarters, regional and country offices, is prepared to provide technical advice and advocacy for the adoption of a donations policy and its implementation, particularly in the areas of information dissemination, policy adoption, advocacy with donors as to the suitability of donations, training, monitoring of implementation, and to provide a rapid response for investigation, analysis, and resolution of reports of adverse events reported in conjunction with the use of donated vaccines.